then increased at 24 h along with an increase in FXR. Geranylgeraniol abolished the effects of pitavastatin on apo A-I, PPARα, and FXR, but enhanced the induction of CYP7A1 mRNA by pitavastatin, suggesting the existence of factors that regulate CYP7A1 in the non-sterol/geranylgeranyl diphosphate (GGpp) pathway. However, the inhibition of Rho-kinase by Y27632 enhanced the effects of pitavastatin on the induction of mRNA levels of apo A-I, PPARα, and FXR, but not that of CYP7A1, suggesting that PPARα may not be a major factor that regulates CYP7A1.
Conclusions: Pitavastatin increases CYP7A1 mRNA levels in HepG2 cells, suggesting that increased conversion of cholesterol into bile acids may be a mechanism for the potent LDL-C-lowering effects of pitavastatin. Increased CYP7A1 mRNA levels by pitavastatin are the net effect of the induction of CYP7A1 by the inhibition of cholesterol synthesis and the suppression of CYP7A1 by inhibition of the non-sterol /GGpp pathway.

1083-191 Biphasic Regulation of STAT1alpha Expression in Vascular Smooth Muscle Cells by Oxidized Low-Density Lipoprotein

Koichi Ono, Sergiy Sukhanov, Yao Hua Song, Patrick Delafontaine, Tulane University School of Medicine, New Orleans, LA

Atherosclerosis is a pro-inflammatory disease involving the effects of many cytokines and growth factors, that signal via distinct pathways, such as the janus kinases (JAKs) and signal transducers and activators of transcription (STAT). Oxidized LDL (OxLDL) is critical for atherosclerotic plaque generation and progression. To examine potential regulation of STAT1a by OxLDL in vascular smooth muscle cells (VSMC), we incubated VSMC with 0-100 microg/ml OxLDL or native LDL (nLDL) and measured STAT1a expression by real-time PCR and Western blotting. OxLDL, but not nLDL, dose-dependently increased STAT1a expression at 3h (51+-1% mRNA increase; 23+-1% protein increase n=3, p<0.01), but markedly reduced STAT1a expression at later time points (89.7+-6.7% decrease in protein levels at 9hr). To determine intracellular signaling pathways mediating OxLDL effects on STAT1a expression, we studied the role of candidate proteins implicated in OxLDL signaling. OxLDL components are high-affinity ligands for PPAR-gamma (PPAR-g), but the effect of OxLDL was not blocked by the PPAR-g inhibitor PGF2a and the synthetic PPAR-g ligand ciglitazone did not regulate STAT1a expression. Furthermore, inhibition of the p38 MAPK pathway (SB203580) or p42/44 MAPK pathway (PD98059) did not modify OxLDL effects, indicating that the ability of OxLDL to regulate STAT1a was not mediated via a p38 or p42/44 MAPK dependent pathway. Likewise, inhibition of the ubiquitin/proteasome pathway (MG132) did not blunt OxLDL regulation of STAT1a. However, 40nM Fucoidan (a scavenger receptor A inhibitor) and Anti-CD36 antibody (a scavenger receptor B inhibitor) markedly blocked OxLDL regulation of STAT1a expression (64%, 71% inhibition, respectively). Furthermore, the water-soluble Vitamine E derivative, Trolox, completely inhibited OxLDL regulation of STAT1a. In conclusion, OxLDL causes biphasic regulation of VSMC STAT1a expression via a PPAR-g, p38 MAPK, p42/44 MARK-independent and redox-dependent pathway that is mediated via scavenger receptors type A and B. These findings have important implications for understanding cellular signaling events regulated by OxLDL, and hence mechanism of atherogenesis.

1083-192 Large Oligomeric Grape Skin Polyphenolics Are Most Effective as Antioxidants and Antiplatelet Agents

Mark R. Beahm, Dhanansayan Shanmuganayagam, Areyl D. Goff, Christian G. Krueger, Jess D. Reed, John D. Folts, University of Wisconsin Medical School, Madison, WI, University of Wisconsin - Madison, Madison, WI

Background: Grape skin polyphenolics (PP) exhibit antioxidant and antiplatelet effects, which may reduce the risk of CVD in individuals consuming them. As these PP are chemically diverse, it is unknown which classes of PP are most effective. We hypothesized that different classes of PP will be differently effective as antioxidants and antiplatelet agents.
Methods: We fractionated a grape skin extract into 6 distinct PP fractions (F1-6; normalized to 5μM gallic acid equivalents of redox potential) using multiple solvent elutions through a Sephadex LH-20 column. F1-6 were characterized using HPLC and MALDI-TOF mass spectrometry. Antioxidant effect was determined by measuring the ability of F 1-6 and ascorbate (control) to extend the lag time to Cu^{2+}-induced oxidation of LDL (n=5): 1) by direct incubation (DI) with the LDL, and 2) by incubating LDL with the compounds and then washing the LDL to remove unbound compounds (TW). Antiplatelet effect was measured using collagen induced whole blood platelet aggregation (PA).
Results: F1-3 contained oligosaccharides, hydroxycinnamic acids, anthocyanins, flavanols and low-MW polygalloyl polyflavan-3-ols (PGPF). F4-6 contained PGPF with 4-8, 5-10, and 6-16 degrees of polymerization, respectively. In DI study, F1-3 extended lag time to LDL oxidation by 64±4%, 156±3%, 147±4%, but failed to retain this effect in the TW study. F1-2 had no effect on PA, however F3 significantly stimulated PA by 31±6%. F4-6 extended DI lag time by 158±1%, 113±7%, and 144±2% and retained 80%, 100%, and 100% of this effect in TW, respectively. F4-6 significantly inhibited PA by 55±14%, 98±0%, and 99±0%, respectively.
Conclusions: F5-6, containing PGPF with 5-16 degrees of polymerization, were most effective as antioxidants and antiplatelet agents. They were also most effective at binding LDL. This suggests that large MW PGPF may be primarily responsible for the beneficial effects of grape skin PP. Conversely, certain PP, such as F3, which stimulated PA, may have undesirable effects on CVD risk factors. Careful study of various classes of PP in a diet may be crucial in determining the overall effect of the PP on CVD.

POSTER SESSION

1084

Lipid Intervention: Statins

Monday, March 08, 2004, Noon-2:00 p.m.
Morial Convention Center, Hall G
Presentation Hour: 1:00 p.m.-2:00 p.m.

1084-168 Multidrug Resistance-1 Gene Polymorphisms Influence the Response to Atorvastatin Treatment in a Gender Specific Manner

Kouji Kajinami, Noboru Takekoshi, Margaret E. Brousseau, Jose M. Ordovas, Ernst J. Schaefer, Kanazawa Medical University, Uchinada, Japan, Tufts University, Boston, MA

*Background:*The mechanisms responsible for interindividual variations in response to statin therapy remain uncertain. Proteins involved in the drug metabolizing system may influence the plasma concentration of statins, and ultimately, plasma lipid levels. *Objectives:*To test the hypothesis that genetic variation in the multidrug resistance-1 (*MDR1*) gene, which encodes for P-glycoprotein that serves as a drug efflux pump, influences the plasma lipid response to statin therapy. *Methods*: Two prevalent *MDR1* polymorphisms (G2677T/A and C3435T) were examined in 344 hypercholesterolemic patients treated with atorvastatin 10mg. *Results:* In women, homozygosity for the 3435C wild type allele was significantly and independently associated with smaller reductions of low-density lipoprotein (LDL) cholesterol (-35±10% vs. -39±8%, p=0.023), but with larger increases of high-density lipoprotein (HDL) cholesterol (+12 ±14% vs. +7±11%, p=0.023), when compared to subjects carrying at least one variant allele. The G2677T/A polymorphism was not associated with treatment response. In women, homozygotes for the wild type haplotype (2677G and 3435C) experienced significantly smaller reductions in LDL cholesterol levels, as compared to subjects carrying the variant haplotype. Furthermore, in women, the increase in HDL cholesterol seen with atorvastatin treatment diminished in accordance with the number of variant haplotypes in a gene-dose dependent manner (p=0.042 for trend). *Conclusions:* In patients with hypercholesterolemia, the *MDR1* C3435T polymorphism is significantly and independently associated with the response to atorvastatin in a gender-specific manner. Haplotype analysis enabled us to identify a subgroup that showed a striking response to treatment, which was not defined by single polymorphism analysis.

1084-169 Efficacy and Safety of Ezetimibe Coadministered With Simvastatin Versus Simvastatin Alone in Thiazolidinedione-Treated Patients With Type 2 Diabetes Mellitus

Linda Gaudiani, Andrew Lewin, Luigi Meneghini, Inna Perevozskaya, Jonathan Tobert, Diane Plotkin, Yale Mitchel, Sukrut Shah, Marin Endocrine Associates, Greenbrae, CA, Merck Research Laboratories, Rahway, NJ

Background: In patients with type 2 diabetes mellitus (T2DM) who are at high risk of coronary heart disease, combination therapy is often required to regulate glucose metabolism and to attain aggressive target levels of low-density lipoprotein cholesterol (LDL-C). The marketed thiazolidinediones (TZD) improve glycemic control and have minimal effects on blood lipids. Ezetimibe (EZE), a novel intestinal cholesterol absorption inhibitor, has a complementary mechanism of action to statins, which inhibit hepatic cholesterol synthesis. We compared the safety and lipid-modifying effects of adding EZE to simvastatin (SIMVA) versus doubling the dose of SIMVA in TZD-treated T2DM patients.
Methods: This was a randomized, double-blind, parallel group, multicenter study in T2DM patients (HbA1c ≤9%), 30-75 years, with LDL-C ≥ 100 mg/dL, and stabilized on a TZD for ≥ 3 months. Patients received open-label SIMVA 20 mg/d for at least 6 wks, and then were randomized in a double-blind manner to either EZE 10 mg/d (n=104) or SIMVA 20 mg/d (n=110), added to ongoing open-label SIMVA 20 mg/d for 24 weeks. Patients were stratified according to TZD type and dose (pioglitazone 15-30 vs 45 mg/d; rosiglitazone 2-4 vs 8 mg/d).
Results: After 6 wks of open-label SIMVA 20 mg, mean (SD) LDL-C values for the EZE+SIMVA and SIMVA only groups, respectively, were 93.7 (28.5) and 91.4 (24.3) mg/dL. LDL-C was reduced more (p<0.001) by adding EZE 10 mg to SIMVA 20 mg (-20.8%) than by doubling the dose of SIMVA to 40 mg (-0.3%). EZE+SIMVA 20 mg also produced significant reductions in non-HDL-C (-20.0%; p<0.001), VLDL-C (-16.3%; p<0.001), and apo B (-14.1%; p<0.001). Triglyceride and HDL-C were not changed significantly by either treatment beyond the levels achieved on open-label SIMVA 20 mg. There were no significant differences in safety parameters between the treatment groups.
Conclusions: Coadministration of EZE with SIMVA, a treatment strategy that affects cholesterol synthesis and absorption, provides greater efficacy than doubling the dose of SIMVA in T2DM patients with mildly elevated LDL-C. The combination of EZE plus SIMVA is a well-tolerated and efficacious treatment option for lowering LDL-C in T2DM patients taking TZDs.

1084-171 Initial Response to Statin Therapy Predicts Response to Dose Titration

Mateen Akhtar, Kirk L. Peterson, Paul S. Phillips, Ori Ben-Yehuda, University of California, San Diego, La Jolla, CA

Background: NCEP guidelines recommend dose titration in patients who have not achieved LDL goal at starting dose. We hypothesized that initial response to statin therapy would predict response to dose titration.
Methods: Retrospective study of 76 adult patients with CAD who met criteria for statin therapy per ATP III guidelines and were treated at initial statin dose followed by dose titra-

tion. Patients were divided into good responders (GR) or poor responders (PR) based upon % change in LDL-C from baseline after initial statin dose.
Results: At baseline, PR had lower total cholesterol (TC) (227±35 vs 258±36 mg/dl;p<0.001) and lower LDL-C (149±29 vs 173±28 mg/dl; p<0.001). Initial change in LDL-C was -30.8±8.7% in GR vs. -8±7.2% in PR (p<0.01). Dose titration led to an additional 14.7±9.4% reduction in LDL-C in GR vs. only additional 7.7±11.6% in PR (p<0.001). After dose titration, PR had less change from baseline in LDL-C (-15.7±14.6% vs -45.5±12%; p<0.001). After dose titration, 18% of PR achieved LDL goal compared to 71% of GR (p<0.001). % LDL-C decrease after dose titration correlated with initial response (r^2=0.72).
Conclusions: Response to initial statin dose predicts response to dose titration. Dose titration of statins is therefore not an effective strategy to reach aggressive LDL goals in patients who have a poor initial LDL reduction. Other approaches such as combination therapy need to be evaluated in this group of patients.

LDL-C response in GR vs. PR

	Good Responders (n=38)	Poor Responders (n=38)	
Change in LDL-C after initial dose	-30.8±8.7%	-8.07.2%±	p<0.001
Change in LDL-C after dose titration (from baseline)	-45.5±12%	-15.7±14.6%	p<0.001
% at ATP III Goal	71%	18%	p<0.001

1084-172 Rosuvastatin Is Efficacious as Monotherapy in Patients With Combined Dyslipidemia

Fahim Abbasi, James W. Chu, Cindy Lamendola, Tracey McLaughlin, Valerie Cain, Howard G. Hutchinson, Gerald M. Reaven, Stanford University, Stanford, CA

Cardiovascular disease (CVD) risk is greater in patients with combined dyslipidemia (CDL) than in those with isolated increases in fasting plasma triglyceride (TG) or low-density lipoprotein (LDL) cholesterol (C) concentrations. Effective treatment (Rx) of CDL has been confounded by: 1) concern of the increased risk of myopathy associated with combined use of a "statin" and a fibric acid; and 2) neglecting the effect of Rx on post-prandial (PP) lipemia. This study was initiated to test the hypothesis that the magnitude of improvement in both fasting and PP lipid metabolism in rosuvastatin (RSV)-treated subjects with CDL would obviate the need for combined drug Rx. Forty nondiabetic subjects with CDL were randomly assigned to Rx with either RSV (40 mg/day) or gemfibrozil (GEM, 1200 mg/day) for 3 months, and multiple aspects of fasting and PP carbohydrate and lipid metabolism measured before and after Rx. The two groups did not differ in age, sex distribution, or BMI. Mean±SE (mg/dL) fasting plasma LDL-C levels fell (P<0.001) following RSV-Rx (138±7 vs. 62±4), but did not change in GEM-treated subjects (126±5 vs. 131±5). Fasting TG levels fell (P<0.001), and to a similar degree in GEM-treated (284±17 vs. 166±23) and RSV-treated (324±19 vs. 211±18) subjects. RSV-treated subjects also had significantly greater decreases in apo B-100, apo E, and the apo B-100/apo A-1 ratio compared to those treated with GEM. Daylong glucose, insulin, and free fatty acid levels did not change with Rx, whereas PP-TG levels fell to a similar degree in both groups (P<0.01). Although the PP-remnant lipoprotein-C levels fell significantly with Rx in both groups, the magnitude of the change was greater in the RSV-Rx group (P<0.05). Finally, RSV-Rx resulted in significant (P<0.001) reductions in C-reactive protein (median change -57.6%) compared to GEM-Rx (median change -9.1%). Conclusion: In addition to the expected substantial decrease in LDL-C, the improvement in both fasting and PP concentrations of TG-rich lipoproteins in RSV-treated subjects was equal to or greater than that seen with GEM-Rx. These results demonstrate that RSV provides effective monotherapy to decrease lipoprotein-related CVD risk factors in subjects with CDL.

1084-173 Analysis of the Renal Safety of Atorvastatin in a Broad Spectrum of Patients With Dyslipidemia

William Sasiela, Halit Silbershatz, Michael Szarek, Pfizer Inc, New York, NY

Background: This report summarizes the renal safety data from >9000 patients exposed to atorvastatin for up to 2 years in completed clinical trials. These data are especially important in the current climate which has seen increased scrutiny placed on all aspects of the safety of chronic statin therapy.
Methods: Data were analyzed from 16,731 dyslipidemic patients (9976 male/6755 female; median age 61 yrs) enrolled in 44 clinical trials. The studies included 9416 atorvastatin-treated patients, 1789 placebo-treated patients and 5526 patients treated with other statins (simvastatin [2771]; pravastatin [807]; lovastatin [968]; fluvastatin [744]; cerivastatin [236]). A broad spectrum of dyslipidemic patients with varying risks for cardiovascular events were evaluated for up to 2 years.
Results: Across the 44 studies analyzed, renal adverse events were rare in all 3 treatment groups. Albuminuria was observed in 7 patients receiving atorvastatin (0.07%), compared to 5 patients receiving other statins (0.09%) and 0 patients receiving placebo. No case of albuminuria was considered to be treatment related. The rate of occurrence of hematuria was also low in all treatment groups (atorvastatin, 44 patients [0.5%]; other statins, 34 patients [0.6%]; placebo, 3 patients [0.2%]). Only in 1 atorvastatin and 1 placebo patient was hematuria considered to be possibly associated with study treatment. In the subset of patients treated in placebo-controlled trials, there were no cases of albuminuria for either placebo or atorvastatin and hematuria was observed in 0.2% of patients treated with placebo (3/1789) and in 0.3% of patients treated with atorvastatin (8/2976). Overall, renal adverse events did not appear to be dose-related, and there were no discontinuations considered related to renal adverse events.
Conclusion: Specific analysis of renal adverse events in 44 clinical trials demonstrates that these occurred infrequently with atorvastatin and at similar rates to placebo. These data provide further evidence to support the favorable clinical safety profile of atorvastatin 10 mg to 80 mg in a broad range of patients.

1084-174 Efficacy of Ezetimibe-10 mg/Day Coadministered With Multiple Doses of Simvastatin in Patients With Primary Hypercholesterolemia

Anne C. Goldberg, Rachel Capece, Aditi Sapre, Ji Liu, Yale Mitchel, Washington University, St. Louis, MO, Merck Research Laboratories, Rahway, NJ

Background: The cholesterol absorption inhibitor, ezetimibe (EZE), has a complementary mechanism of action to statins, which inhibit hepatic cholesterol synthesis. The purpose of this study was to evaluate the LDL-C-lowering efficacy of EZE 10 mg/d coadministered with simvastatin (SIM) 10, 20, 40, and 80 mg/d in hypercholesterolemic patients (pts).
Methods: This was a 12 wk multicenter, double-blind, randomized, placebo (PBO)-controlled study. After a 4-wk PBO/diet run-in, 887 pts with LDL-C 145 - 250 mg/dL and TG ≤350 mg/dL were randomized to one of ten daily treatments: PBO; EZE 10 mg; SIM 10, 20, 40, or 80 mg; EZE 10 mg + SIM 10, 20, 40, or 80 mg.
Results: Results for LDL-C, non-high density lipoprotein cholesterol (non-HDL-C), triglycerides (TG), and HDL-C by dose are summarized in the table. Pooled across the dose ranges, EZE+SIM was more effective (p ≤0.001) than SIM in reducing LDL-C (-53.1% vs. -38.3%), TG (-28.0% vs. -15.2%) and non-HDL-C (-48.5% vs. -34.1%), while HDL-C was increased by 8% in both groups. A greater proportion of EZE+SIM pts reached the LDL-C target of <100mg/dL (p <0.001): 82.4% (n=353) vs. 42.9% (n=345). Coadministration of EZE+SIM was well tolerated and had an overall safety profile similar to that of SIM monotherapy. However, there were more cases of consecutive ≥3 x upper limit of normal elevations of aminotransferases in the EZE+SIM group vs. SIM group.
Conclusions: Overall, EZE+SIM was well tolerated and provided superior lipid-modifying efficacy over SIM monotherapy.

Mean Percent Change from Baseline

Lipid Parameter	SIM 10mg (n=79)	EZE/SIM 10mg/10mg (n=87)	SIM 20mg (n=89)	EZE/SIM 10mg/20mg (n=86)	SIM 40mg (n=90)	EZE/SIM 10mg/40mg (n=89)	SIM 80mg (n=87)	EZE/SIM 10mg/80mg (n=91)

									LDL-C	-31.3	-46.2	-34.9	-50.5	-41.5	-54.9	-45.6	-60.8
Total C	-20.7	-31.5	-24.1	-36.5	-28.7	-39.5	-31.7	-43.0									
non-HDL-C	-26.8	-41.3	-31.2	-47.1	-37.0	-50.9	-41.4	-54.8									
TG (median)	-4.5	-20.5	-13.6	-30.7	-18.6	-32.0	-25.7	-27.8									
HDL-C	4.9	9.5	6.3	8.0	8.3	9.1	11.0	6.3									

1084-175 Changes in Coronary Plaque Color and Morphology by Lipid-Lowering Therapy With Atorvastatin: Serial Evaluation by Coronary Angioscopy

Masamichi Takano, Kyoichi Mizuno, Shigenobu Inami, Fumiyuki Ishibashi, Kentaro Okamatsu, Koji Seimiya, Takayoshi Ohba, Shinya Yokoyama, Shunta Sakai, Noritake Hata, Nippon Medical School, Chiba, Japan, Chiba-Hokusoh Hospital, Chiba, Japan

Background: The concept of coronary plaque stabilization by statin therapy has been clarified. However, serial changes of coronary plaques by statin therapy in human have not been examined in detail.
Methods: Thirty-one patients with coronary artery disease were devided into either the comparison group (n=16) or the atorvastatin group (n=15). Before treatment and 12 months after, the color and complexity of 145 coronary plaques were determined according to angioscopic findings. The yellow score of the plaque was defined as 0 (white), 1 (light yellow), 2 (yellow), or 3 (dark yellow), and its disrupted score was defined as 0 (smooth surface) or 1 (irregular surface) and as 0 (without thrombus) or 1 (with thrombus). In each patient, the mean yellow score and mean disrupted score were calculated.
Results: Mean low-density lipoprotein cholesterol (LDL-C) decreased by 45% in the atorvastatin group, whereas an increase of 9% was seen in the comparison group. The mean yellow score decreased from 2.03 to 1.13 in the atorvastatin group, whereas it increased from 1.67 to 1.99 in the comparison group. There was a good correlation between the change in the mean yellow score and the change in LDL-C levels (r=0.81, p<0.0001). The change in the mean yellow score and mean disrupted score differed significantly between the two groups (p=0.002 and p=0.03, respectively).
Conclusions: This study indicated that lipid-lowering therapy changes plaque color and morphology and should then lead to coronary plaque stabilization.

1084-176 Efficacy of Ezetimibe Coadminstered With Simvastatin Versus Atorvastatin in Patients With Hypercholesterolemia

Christie M. Ballantyne, Michael A. Blazing, Thomas R. King, William E. Brady, Joanne Palmisano, Merck & Company, Inc., West Point, PA

Background: This study was designed to evaluate the efficacy and safety of ezetimibe coadministered with simvastatin (EZ/S) vs atorvastatin (A) in adults with hypercholesterolemia.
Methods: After a four-week diet/placebo run-in period, eligible patients were randomized 1:1:1 to 3 treatment groups, each for four 6-week periods: (1) A10 mg titrated to A20 mg, A40 mg, and A80 mg through Periods 1-4; (2) EZ/S 10 mg (10/10) titrated to EZ/S 20 mg